NON-FINAL REJECTION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed 7/16/2009.

Claim 12 has been cancelled.

Claims 1-4 and 11 have been amended and incorporate no new matter.

No new claims have been added.

Thus, claims 1-11, 16, and 22-26 now represent all claims currently pending and under examination.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been submitted.

WITHDRAWN OBJECTIONS/REJECTIONS

Objections

Due to the amendments to the claims, the objection to claim 11 is withdrawn.

Rejections under 35 USC §102(b)

Due to the amendments to the claims, the rejection of claims 1-11 under 35 USC 102(b) as anticipated by Masferrer et al. is withdrawn.

Rejections under 35 USC §103

Due to the amendments to the claims, the rejection of claims 22, 23, 25, and 26 under 35 USC 103(a) as obvious over Masferrer et al. in view of Heinrichs is withdrawn.

Due to the amendments to the claims, the rejection of claim 24 under 35 USC 103(a) as obvious over Masferrer et al. is withdrawn.

MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Action dated 4/16/2009, on the ground that the references cited therein continue to read on the limitations of the amended claims.

Rejections under 35 USC §103

Claim 16 stands rejected under 35 USC 103(a) as obvious over Masferrer et al. in view of Riendeau et al. In addition, due the amendments to claim 1, this rejection is extended to claims 1-11.

RESPONSE TO ARGUMENTS

With respect to the rejection of claims 1-11 and 16 as obvious over Masferrer et al. in view of Riendeau et al., in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction

based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant notes that the compounds of formulae (I) and (II) disclosed by Masferrer et al. do not encompass etoricoxib (see Remarks dated 7/16/2009, p. 8). However, the compounds of formulae (I) and (II) are merely preferred embodiments of selective COX-2 inhibitors. The disclosed methods of treating endometriosis are not limited to these or exclusive of all other COX-2 inhibitors. Indeed, Masferrer et al. identifies compounds which selectively inhibit COX-2 disclosed in other references (p. 2, lines 21-29), and describes the functional benefits of selective COX-2 inhibition without regard to the structure of the compound (see, e.g., p. 3, lines 10-26).

Applicant also correctly notes that Riendeau et al. do not disclose the administration of etoricoxib in the treatment of endometriosis (see Remarks dated 7/16/2009, p. 8). However, Masferrer et al. describe the functional benefits of selective COX-2 inhibition in the treatment of endometriosis, and Riendeau et al. disclose that etoricoxib is the most highly selective inhibitor of COX-2 over COX-1. Thus, one of ordinary skill in the art would have been motivated to employ etoricoxib in the methods of Masferrer et al. with a reasonable expectation of success, with the added advantage of reduced side effects resulting from minimal COX-1 inhibition.

As recognized by MPEP §2144 (II), the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

NEW REJECTIONS

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-11, 16, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating certain conditions, does not reasonably provide enablement for *preventing* the claimed conditions. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims without undue experimentation. MPEP 2164.01(a), citing *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), sets out the factors to consider whether experimentation is undue, which include:

(A)The breadth of the claims. The specification does not define the term “treating,” which is reasonably interpreted to include any measure taken to reduce, relieve, or ameliorate an existing condition. The specification also does not define the term "preventing," which is reasonably interpreted to include any measure taken prior to the development of a condition which precludes its coming into existence. While “treating” is supported by the disclosure, the term “preventing” is unreasonably broad.

(B) The nature of the invention. The claims are drawn to methods of treating or preventing endometriosis, and reducing aromatase levels, by administering a COX-2 inhibitor, in combination with an oral contraceptive or with a GnRH agonist.

(C) The level of predictability in the art. “Prevent” connotes an absolute absence of a condition which cannot reasonably be achieved with regard to the claimed conditions, or in medicine generally, with few exceptions (such as vaccines to prevent the development of pathogen-borne illnesses). In addition, there is no definitive method by which to determine whether a patient would develop the claimed conditions and, thus, be in need of preventive therapy. Even if a patient can be identified as having known risk factors for a disease, there is no certainty that a patient would in fact develop that disease. Further, the failure of a condition to develop cannot reliably be attributed to the active agent; for example, the condition may reverse or resolve due to other factors such as diet, exercise, lifestyle, or genetics. Thus, the term "preventing” is unreasonably broad and unsupported by the disclosure.

(D) The amount of direction provided by the inventor. While the specification provides examples of formulations intended for use in the claimed methods (Examples 1-6), no specific embodiments or working examples in which the claimed conditions are *prevented* are disclosed or tested.

(E) The quantity of experimentation needed to make or use the invention. Because "preventing" a condition by the administration of an active agent cannot be objectively measured or achieved with any certainty, coupled with a lack of guidance and direction provided by the instant disclosure, a skilled artisan could not practice the invention commensurate with the full scope of the claims without undue experimentation.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-11, 16, and 24-26 are rejected under 35 U.S.C. 102(e) as being anticipated by DiSalle et al. (WO02/72106).

DiSalle et al. disclose methods of treating and preventing hormone-dependent disorders, in particular endometriosis and endometrial hyperplasia, comprising administering to a patient in need thereof the aromatase inactivator exemestane, alone

or in combination with additional therapeutic agents (p. 1, lines 5-10). Preferably, there are two additional therapeutic agents (p. 6, lines 16-18), which may include

- a COX-2 inhibitor, preferably celecoxib, rofecoxib, valdecoxib, and compound MK-663 (a.k.a. etoricoxib) (p. 17, lines 7-13), as recited by claims 1 and 16; and
- a GnRH agonist, preferably leuprorelin (a.k.a. leuprolide acetate, p. 19, lines 15-29), as recited by claims 25 and 26.

In the combination therapy disclosed by DiSalle et al., the compounds may be co-administered sequentially, in either order (p. 23, lines 16-23), as recited by claims 25 and 26.

The methods of DiSalle et al. are disclosed to give relief from pain accompanying hormone-dependent disorders, in particular in patients suffering from endometriosis. The methods include improving the endometriosis pain symptoms of dismenorrhea, dyspareunia, and pelvic pain, in a patient suffering from endometriosis (p. 22, lines 18-25). In addition, DiSalle et al. disclose that the aims of treatment of a patient with endometriosis include elimination of the misplaced endometriotic tissue and the relief of pain. DiSalle et al. note that treatment of endometriosis includes administration of drugs that suppress the activity of the ovaries and slow the growth of endometrial tissue, surgery to remove the misplaced endometriotic tissue, surgical removal or the uterus, fallopian tubes and/or ovaries, or combinations of those treatments (p. 2, lines 11-21).

Thus, DiSalle et al. explicitly disclose methods of treating or preventing endometriosis, as recited by claim 1. By treating and preventing endometriosis, these

methods also implicitly disclose retarding, preventing, and reversing the development of endometriotic lesions of a type amenable to hormonal therapy, as recited by claims 2-4 and 6-8; and reducing the number and severity of endometriotic lesions, as recited by claim 5. By combining the administration of drugs to slow the growth of endometrial tissue with surgery to remove the misplaced endometriotic tissue, DiSalle et al. also implicitly disclose a method comprising administering a COX-2 inhibitor perioperatively or as a follow-up therapy to surgical removal of endometriotic implants, as recited by claim 24.

Alternatively, the claimed methods are inherent in the methods of DiSalle et al; that is, carrying out the methods taught by the reference inherently results in the claimed methods. See MPEP §2112.

While the instant claims do not recite the administration of exemestane, as taught by DiSalle et al., the claimed methods *comprise* the administration of a COX-2 inhibitor, specifically celecoxib, rofecoxib, and valdecoxib (p. 26, line 21 to p. 27, line 7), as recited by claim 1.

Therefore, DiSalle et al. anticipates claims 1-11 and 24-26.

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1 and 22, 23, 25, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over DiSalle et al. (WO02/72106), in view of Heinrichs (US Pat. 6,265,393, cited in the Office Action dated 4/16/2009).

As discussed above, DiSalle et al. disclose methods of treating and preventing endometriosis, comprising the administration of exemestane in combination with additional therapeutic agents, which may include

- a COX-2 inhibitor, preferably celecoxib, rofecoxib, valdecoxib, and compound MK-663 (a.k.a. etoricoxib) (p. 17, lines 7-13), as recited by claims 1 and 16; and
- a GnRH agonist, preferably leuprorelin (a.k.a. leuprolide acetate, p. 19, lines 15-29), as recited by claims 25 and 26.

In the combination therapy disclosed by DiSalle et al., the compounds may be co-administered sequentially (p. 23, lines 16-23), as recited by claims 25 and 26.

Thus, DiSalle et al. explicitly disclose methods of treating or preventing endometriosis, as recited by claim 1. By combining the administration of drugs to slow the growth of endometrial tissue with surgery to remove the misplaced endometriotic tissue, Alternatively, the claimed methods are inherent in the methods of DiSalle et al; that is, carrying out the methods taught by the reference inherently results in the claimed methods. See MPEP §2112.

While DiSalle et al. teach the administration of the claimed selective COX-2 inhibitors in the treatment and prevention of endometriosis, the reference does not teach the concomitant or sequential co-administration of an oral contraceptive, as recited by claims 22 and 23.

Heinrichs teaches a method of treatment and prevention of endometriosis symptoms and the recurrence thereof (col. 4, lines 15-39) by the administration of a gonadotropin-releasing hormone (GnRH) agonist, to include leuprolide acetate (col. 9, lines 30-35), followed by the co-administration of an estrogen agent and a progestin agent such as norethindrone. (col. 8, lines 30-45; Table 2).

One of ordinary skill in the art would have been motivated to combine the methods of treating endometriosis comprising the co-administration of the COX-2 inhibitor etoricoxib and the GnRH agonist leuprolide acetate, as taught by DiSalle et al., with the methods of treating endometriosis comprising the co-administration of the GnRH agonist leuprolide acetate and the progestin (oral contraceptive) norethindrone as taught by Heinrichs, because, as recognized by MPEP §2144.06, "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Further, as recognized by MPEP §2143, combining prior art elements according to known methods to yield predictable results would motivate the skilled artisan to modify the references with a reasonable expectation of success. The rationale to support a conclusion of prima facie obviousness is that all the claimed elements were known in the prior art, and a skilled artisan could have combined the elements as claimed by known methods with no change in their respective functions, and the

combination yielded nothing more than predictable results to one of ordinary skill in the art. See *KSR Int'l Co. v. Teleflex Inc*. (550 U.S. 398, 409).

CONCLUSION

Claims 1-11, 16, and 22-26 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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